The Role of Target Therapy in the Treatment of Gastrointestinal Noncolorectal Cancers: Clinical Impact and Cost Consideration

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Abstract: Gastrointestinal (GI) tumors are among the leading cause of death in cancer patients worldwide. Particularly, gastric cancer (GC) is the third cause of cancer deaths, whereas esophageal neoplasm is the eighth leading most common cancer worldwide and its incidence, especially adenocarcinoma type, is continuously increasing. Also, Hepatocellular carcinoma, Cholangiocarcinoma and pancreatic cancer represent a very interesting model to multidisciplinary approach and recently new drugs are used in their treatment. Currently, new clinical trials are designed including classic chemotherapy in association with either small molecule inhibitors (*i.e.* Tyrosine Kinase inhibitors) and/or monoclonal antibody (*i.e.* anti-EGFR antibody). Moreover, a comprehensive list of new molecules for target therapy is included in this issue. The development of new treatment modalities (multidisciplinary approach) and targeted therapy approaches have contributed to improving the outcome in these cancer diseases. During the past few years, remarkable progress in molecular biology of malignancy, the discovery of specific targets, and the resulting development of systemic drugs that block critical kinases and several molecular pathways have all contributed to progress in cancer treatment, also in GI non-colorectal cancer treatment.

Keywords: Gastrointestinal cancers, target therapy, clinical aspects, treatment, prognostic factors, metastases, costs.

1. INTRODUCTION

Gastrointestinal (GI) tumors are among the leading cause of death in cancer patients worldwide. Particularly, gastric cancer (GC) is the third cause of cancer deaths [1] whereas esophageal neoplasm is the eighth leading most common cancer worldwide and its incidence, especially adenocarcinoma type, is continuously increasing [2]. At the same time, colorectal cancer (CRC) is the third most common cancer worldwide [3]. In 2013, about 30,000 new cases of liver cancer have been estimated in the United States population [4]. Similarly, more than 45,000 new diagnosed cases of pancreatic cancer have been estimated in the US in 2014 while its survival rate hardly improved in the last three to four decades [4]. The development of new treatment modalities (multidisciplinary approach) and targeted therapy approaches have both contributed to improving the outcome in these cancer diseases. Based on new knowledge of molecular features of the tumor, it is urgently needed to clarify some aspects of new treatments. The aim of this review is to summarize the role of target therapies in the treatment of gastrointestinal noncolorectal Cancers. New biological agents with molecularly targeted therapies, currently included in clinical trials are reported below (Table **1**).

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2. GASTRIC CANCER

Gastric cancer (GC) is the fifth most common cancer and third leading cause of cancer-related deaths worldwide. More than 21,000 patients are diagnosed every year in the United States, and about 11.000 are expected to die [1]. Despite medical progress in both early diagnosis and in new therapeutic strategies, GC remains a prevalent disease worldwide with a poor prognosis, with less than 20% of subjects diagnosed with gastric cancer survive for more than 5 years [1]. In the metastatic setting chemotherapy (CT) improves overall survival (OS) and also the quality of life (QoL), when compared to best supportive care; however, the median OS remains below 1 year [5]. The understanding of molecular pathways involved in gastric carcinogenesis offers novel treatment options. Several drugs are active in the treatment of GC, including platinum agents, fluoropyrimidines (5-FU, capecitabine, and S1), anthracyclines, taxanes, irinotecan, and some targeted therapies such as trastuzumab for HER-2

overexpressing GCs and ramucimumab. Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer and are associated with better response rates (RR) and survival when compared with single-agent chemotherapies [6]. Triplets containing taxanes are also an evidence-based treatment choice for first-line chemotherapy [7, 8]. In the first line setting docetaxel [7], cisplatin/Oxaliplatin [8], and trastuzumab [9, 10] use is supported by high level of evidence (level 1) for the treatment of GC. In general, the trials evaluating the efficacy of other targeted therapies, such as anti-EGFR and anti-vascular endothelial growth factor (VEGF), were done in unselected (not bio-marker driven) populations and have obtained disappointing results.

Table 1. New biological agents with molecularly targeted therapies, currently included in clinical trials in the treatment of gastrointestinal non colorectal cancer.

• EGFR inhibitors
Erlotinib, Lapatinib, Afatinib, Panitumumab, Cetuximab
• Antiangiogenic agents (*i.e.* anti-VEGFR)
Bevacizumab, Sorafenib, Sunitinib, Cediranib, Ramucirumab
• MEK inhibitors
Selumetinib, MEK162 (ARRY-438162)
• C-MET inhibitors
Cabozantinib, LY2801653, Onartuzumab, Tivantinib.
• IDH inhibitors
AG-120, AG-221
• Mutated BRAF
Ipilimumab
• PD-1 inhibitors
Pembrolizumab
• FGFR2 inhibitors
BGJ398, Ponatinib, Brivanib

Trastuzumab, a monoclonal antibody useful in the HER2 enriched population, is the first drug with target molecular to be used with documented efficacy in the treatment of advanced GC and of the gastroesophageal junction cancer. However, only less than 20% of GCs overexpress HER2, so that a relatively smaller proportion of patients benefits from this medical approach [11].

The phase III ToGA trial, conducted in 584 patients whose tumors overexpressed HER2 by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), demonstrated clinically and statistically significant improvements in OS with the addition of trastuzumab to a cisplatin/fluoropyrimidine doublet (median OS 13.8 versus 11.1 months, HR 0.74, 95% CI 0.60–0.91; P = 0.0048). The CT was administered every 3 weeks for six cycles and trastuzumab was administered every 3 weeks until disease progression [10]. Also secondary endpoints of PFS (6.7 mo *vs* 5.5 mo; p= 0.0002) and RR (47.3% *vs* 34.5%; p= 0.0017) were significantly improved. Based on this results, the combination of trastuzumab to a cisplatin/fluoropyrimidine doublet has become the standard of care in gastric cancer patients with tumors HER2-overexpressed [10]. Recently, the efficacy and safety of intraperitoneal trastuzumab in patients with peritoneal carcinomatosis from GC with HER2 3+ have been reported. The treatment obtained a control of local disease with good safety [12]. As known, angiogenesis is an important aspect of tumorigenesis in several neoplasms and preliminary studies suggested a clinical benefit of the addition of bevacizumab, a monoclonal antibody against VEGF-A, in combination with CT in GC [13,14]. In the phase III AVAGAST trial, patients with locally advanced or metastatic gastric cancer were randomly assigned to bevacizumab (n = 387) or placebo (n = 387) in combination with chemotherapy. Despite the failure of bevacizumab to improve OS, a careful analysis of subsets allows to note that there is a western population which may derive some benefit [15,16]. In fact, GC subtypes may be important predictors of patients outcome. In the global trial, enrolled patients were Asian (49%), European (32%) or American (19%). When subset analyses were performed in the AVAGAST trial, bevacizumab therapy appeared to improve outcomes in non-Asian patients with type 2 (diffuse GC) and 3 GC (distal non-diffuse GC) [15,16,23]. Another novel antiangiogenic drugs, ramucirumab, a fully human IgG1 monoclonal antibody directed against VEGFR-2, as reported in the REGARD trial, demonstrated modest but statistically significant activity in second-line patients with advanced gastric or gastroesophageal junction adenocarcinoma after progression to first-line platinum or fluoropyrimidine- containing CT [17], with a median OS of 5.2 months for patients in the ramucirumab group *vs* 3.8 months for those in the placebo group (HR = 0.776, 95% CI 0.603–0.998; *P* = 0.047). with an increase in PFS (2.1 months for ramucirumab *vs* 1.3 months for placebo; HR= 0.48, p < 0.0001). The phase III RAINBOW trial investigated the role of ramucirumab (versus placedo) combined with paclitaxel in 655 advanced GC patients in sthe econd line after progression to first-line platinum or fluoropyrimidine- containing CT [18]. The primary endpoint was OS . Median OS was 9.63 months for ramucirumab + paclitaxel compared to 7.36 months for paclitaxel alone (HR = 0.807, 95% CI 0.678–0.962, *P* = 0.017). Median PFS (4.4 months *vs* 2.8 months; HR 0.63, 95% CI 0.53–0.75, p<.0001), and RR (28% *vs* 16%, p < 0.0001) compared to standard treatment. Based on these results, The US Food and Drug Administration (FDA) has recently approved the use of Ramucirumab in combination with Paclitaxel for advanced gastric/GE adenocarcinoma. Thus, this combination has become a standard of care for treatment in the second-line setting for metastatic upper GI tumors. In the first-line setting, ramucirumab combined with FOLFOX in patients with advanced gastric/GE junction tumors did not improve median progression-free survival (PFS) (6.4 versus 6.7 months, HR = 0.98, 95% CI 0.69–1.37, *P* = 0.89) neither OS (11.7 versus 11.5 months, HR = 1.08, 95% CI 0.73–1.58) [19]. Ongoing clinical trials are investigating other combinations of CT with ramucirumab in the first-line setting. Multitarget TKIs, in their roles as antiangiogenic agents, represent another potential approach and had been explored in the treatment of gastric/GE junction tumors. A phase II trial evaluated the role of Sunitinib in patients with advanced gastric or GE

junction tumors after first-line progression to CT [20]. The rate of clinical benefit was 7.7%, and 32.1% of patients obtained stable disease. Median OS was 6.8 months (95% CI 4.4–9.7 months). The addition of docetaxel to sunitinib in another phase II study resulted in a higher rate of objective response (RR 41.1% versus 14.3%, $P = 0.02$) but primary endpoint (prolonging time-to-progression) was not met [21]. In a multicenter phase II study, Sorafenib, another oral multitarget TK-inhibitor, was combined with oxaliplatin after progression on first-line cisplatin/fluoropyrimidine CT [22]. Also, this study did not meet its primary endpoint of efficacy, with median PFS of 3 months (95% CI 2.3–4.1 months) and median OS of 6.5 months (95% CI 5.2–9.6 months). Recent advances in the understanding of GC biology were performed by the Cancer Genome Atlas (TCGA) to identify all the potential gene expression patterns that may justify tumor heterogeneity and which allowed recognizing four distinct genomic disease subtypes of GC that have served as the rationale for the development of novel targeted agents [23]. Dysregulation of the mesenchymal-epithelial transition (MET) signaling pathway is associated with poor prognosis in gastroesophageal adenocarcinoma [23]. The reported rates for MET overexpression and MET amplification are 4% to 98% and 1.5% to 59.0%, respectively [24] and several MET-inhibitors are in clinical development. AMG 337 is a highly selective, orally available MET inhibitor that showed promising preclinical activity. In a phase I open-label trial, 80 patients with MET-amplified cancers defined 300 mg/day as the maximum tolerated dose of AMG 337 monotherapy [26]. Particularly, in 13 heavily pretreated patients with MET-amplified, a remarkable and interestingly fast clinical benefit (within 4 weeks of treatment) associated at 62% rate of response was observed. Rilotumumab (AMG 102) is a monoclonal antibody directed against hepatocyte growth factor, the only known ligand for the MET receptor. In patients with gastric cancer, overexpression of MET, the membrane receptor for HGF, is common and has been associated with lymph-node metastases, higher disease stage, and shortened survival [27]. Rilotumumab in combination with epirubicin, cisplatin and capecitabine as a first-line treatment for gastric or oesophagogastric junction adenocarcinoma was tested in a open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. In this study median PFS was 5.7 months (4.5-7.0) in rilotumumab groups and 4.2 months (2.9-4.9) in the placebo group HR 0.60 (80% CI 0.45-0.79; p=0.016) [28]. Unfortunately RILOMET-1, the corrispective international phase III multicenter, randomized, double-blind, placebo-controlled trial, did not meet its primary endpoint; From November 2012 to November 2014, 609 patients were randomly assigned into the trial, 304 patients received rilotumumab plus ECX and 305 patients received placebo plus ECX. The study was stopped early based on an imbalance in deaths in the fourth preplanned review of safety data (93 deaths in the rilotumumab arm *vs.* 75 deaths in the placebo arm at a data cutoff date of november 3, 2014). OS was statistically significantly worse in Rilotumimab group [29].Results showed that rilotumumab was not superior to placebo for OS; infact median OS was 9.6 months (range: 7.9-11.4 months) in the rilotumumab arm and 11.5 months (range: 9.7-13.1 months) in the placebo arm (HR: 1.36 [1.05,1.75]; P=0.021). In addition, PFS and ORR were statistically worse in the rilotumumab arm. Median PFS was 5.7 months (range: 5.3-5.9 months) in the rilotumumab arm and 5.7 months (range: 5.5-7.1 months) in the placebo arm (HR: 1.27 [1.03,1.58]; P=0.025).Onartuzumab, is a recombinant, fully humanized, monoclonal anti-MET antibody. A phase II trial, evaluating upfront FOLFOX6 with onartuzumab at the dose of 10 mg/kg versus placebo, did not meet his primary end point, PFS (6.77 months in the onartuzumab arm, 6.97 months in the placebo arm; HR 1.08, 95% CI 0.71–1.63) [30]. Particularly, also the preplanned analyses in the MET-positive population generated disappointing results with a median PFS of 5.95 months in onartuzumab arm *vs* 6.8 months in placebo arm (HR: 1.38). A large Phase III trial (METgastric), placebo-controlled trial, testing addition of onartuzumab to mFOLFOX6, was stopped early due to sponsor decision. In the ITT population, onaetuzumab did not significantly improve OS, PFS, or ORR *vs* placebo [31]. It is likely not to consider IHC MET overexpression a good driver for patient selection. Drugs designed to block programmed cell death (PD-1) receptor and its ligands (PD-L1, PD-L2), enhancing antitumor immunity, have demonstrated clinical activity in several types of advanced cancers, validating this pathway as a major methodological approach [32] even in GC because the high expression of PD-L1 on tumor gastric cells [33]. Data of the KEYNOTE-012 gastric cohort phase 1b study, in which pembrolizumab, a highly selective IgG4k, humanized monoclonal antibody against PD-1, was given at 10 mg/kg every 2 weeks to 39 patients with PD-L1-positive advance GC, were recently publisheb. [34]. The trial enrolled heavily pretreated non-Asian (20) or Asian (19) patients, wherein 67% received ≥2 treatment lines. Overall RR was 22% (95% CI 10%-39%) by central review and 33% (95% CI 19%-50%) by investigator review. Authors found also a significant association between PD-L1 expression level and objective RR (one-sided P=0.10). Median progression-free survival as assessed by central review was 1·9 months (95% CI 1.8-3.5). Median OS was not reached, but the 6-month OS rate was surprisingly high (69%). In another study of pemborlizumab, KEYNOTE-028, for the heavily treated esophageal and GEJ carcinoma showed similar response with an ORR of 30.4%, a 6-month PFS rate of 30.4% [35]. On the basis of these results, a Phase III randomized trial that compares pembrolizumab to paclitaxel in patients with recurrent or metastatic gastric or gastro esophageal junction adenocarcinoma who progressed after first-line treatment has been designed. Also Nivolumab, another anti-PD-1 monoclonal antibody, was tested in a phase I/II study (CheckMate-032) in patients with heavily pretreated metastatic gastric or GEJ cancer of PD-L1-positive or –negative tumors [37]. The study demonstrated that nivolumab monotherapy was well tolerated and demonstrated encouraging antitumor activity in this clinical setting.

Similarly, Avelumab, another anti-PD-1 antibody, has shown an early sign of efficacy [36] with ORR of 15% and a 12-week PFS rate of 43.3% advanced gastric cancer [38, 39]. Two large phase III trials with Avelumab in advanced gastric cancer are ongoing. JAVELIN Gastric 100 is a phase III multicentric open-label trial that investigates maintenance therapy after completing an induction phase with a combination of oxaliplatin and a fluoropyrimidine for three months. Patients are randomized to either a maintenance phase with avelumab at the dose of 10 mg/kg or to continuing the same chemotherapy doublet until disease progression, unacceptable toxicity, or consent withdrawal. The co-primary end-

points of the study are overall survival and progression-free survival [40]. JAVELIN Gastric 300 is a third-line study designed to evaluate avelumab immunotherapy as a third-line treatment in advanced or metastatic gastric/gastro-esophageal junction cancers versus chemotherapy (paclitaxel or irinotecan) + BSC or BSC alone per investigator discretion in patients unfit for chemotherapy. The primary endpoint of the study is the overall survival [41].

3. HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the sixth most common and third most lethal neoplasm, with an estimated about 700000 deaths annually worldwide [42]. The principal risk factors of HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, geographic variations, abuse of alcohol obesity, type 2 diabetes and HIV [43-47]. The chronic inflammation, caused by viral hepatitis, is the principal reason of hepatocyte regeneration and accumulation of genetic and/or epigenetic changes and alteration of the liver tumor microenvironment [48]. Patients asymptomatic, with very early or early (stage A) HCCs, are candidates for curative locoregional treatments such as surgical resection, liver transplantation, or radiofrequency ablation-percutaneous ethanol injection (RFA-PEI), with a median OS of about 60 months [42-44, 49]. The discovery of most frequent genomic alterations may provide a possibility to developing a specific targeted anticancer therapy [50]. The current standard therapy for advanced liver cancer is Sorafenib, an oral multi-tyrosin-kinases, which extends the median life of patients by only 1 year. Several new drugs are in the development and several clinical trials are ongoing [51, 52]. In both human HCC tissue and serum samples, the enhanced expression of VEGF is correlated with aggressive phenotype, resulting in a poor prognosis [54]. Furthermore, HCC is an extremely vascularized tumor, and anti-angiogenetic drugs are appealing for the molecular therapy of HCC. Moreover, in HCC patients, also a deregulated c-MET receptor protein generally can result in a poor prognosis [55], and c-MET inhibitors could be a promising treatment for HCC. The principal molecular pathway [52] involved in cell proliferation, apoptosis, metastases and angiogenesis in HCC, are summarized in Fig. (**1**). In Table **2**, the most clinical relevant drugs under investigations for HCC are summarized [69]. Particularly, we mainly described principal molecular targeted agents tested in phase III with advanced HCC patients.

3.1. Sorafenib

Sorafenib is an oral multi-kinase inhibitor that inhibits the activity of Raf-1, B-Raf, VEGFRs 1, 2, and 3 and PDGFR-β [56,57]. The efficacy of sorafenib has been demonstrated in two large randomized controlled trials. In phase III SHARP trial (Sorafenib HCC Assessment Randomized Protocol), 602 patients with advanced, unresectable, measurable HCC, ECOG PS 0-2, Child-Pugh class A, and no prior systemic therapy for HCC were randomized in 1:1 to receive either sorafenib 400 mg BID or placebo. Sorafenib has shown an improvement in OS (10.7 and. 7.9 months in the treatment and placebo arm respectively), (HR0.69; 95% CI, 0.55–0.87; p<0.001) and good safety in patients with HCC [58]. In another phase III Asiatic study, sorafenib was tested on to 271 patients with advanced HCC. The median OS was 6.5 months in the sorafenib group and 4.2 months in the placebo group (HR, 0.68; 95% CI, 0.50–0.93; p<0.014) [59]. Sorafenib is the standard of care for the treatment of patients with advanced HCC.

3.2. Brivanib

Brivanib is an orally active TKI, targeting both FGF and VEGF signaling pathways, closely associated with HCC pathogenesis [60]. In a randomized phase III clinical trial, BRISK-FL study, advanced HCC naive patients were randomly assigned (ratio, 1:1) to receive sorafenib 400 mg twice daily orally (n = 578) or brivanib 800 mg once daily orally (n = 577). Although it did not meet its primary endpoint of OS (non-inferiority trial), brivanib treatment yielded a 9.5 month OS, showing similar antitumor activity to sorafenib (9.9 months of OS) (HR, 1.06; 95% CI, 0.93–1.22; p<0.373) [61]. In the second-line setting, in multicenter, double-blind, randomized, placebo-controlled trial assessing brivanib in patients with HCC who were refractory or intolerant to sorafenib BRISK-PS study, it was proven that brivanib treatment did not improve the OS (mOS 9.4 months for brivanib and 8.2 months for placebo HR, 0.89; 95% CI, 0.69–1.15; p= 0.3307). Exploratory analyses showed a median time to progression of 4.2 months for brivanib and 2.7 months for placebo (HR, 0.56; 95% CI, 0.42 to 0.76; P < .001) [62].

3.3. Sunitinib

Sunitinib is an oral and multitargeted tyrosine kinase inhibitor targeting all VEGFRs, PDGFRs, c-kit, Flt-3 and RET genes. A large phase III trial with a total of 1074 HCC patients was randomized to receive sunitinib 37.5 mg once per day or sorafenib 400 mg twice per day. The result showed the median OS with sunitinib was not superior but was significantly inferior to sorafenib (7.9 versus 10.2 months; HR, 1.30; one-sided p<0.9990; two-sided p<0.0014). OS with sunitinib was OS comparable in Asian and hepatitis B-infected patients. OS was superior in hepatitis C-infected patients who received sorafenib (9.2 versus 17.6 months; HR, 1.52; one-sided p<0.9835) . Sunitinib-treated patients reported more frequent and severe toxicity. [63].

3.4. Erlotinib

Erlotinib, an orally active inhibitor of EGFR tyrosine kinase, showed modest antitumor activity in a phase II clinical trial but present a surprising OS benefit of about 1 year in unresectable HCC patients [64,65]. More recently, in a phase III SEARCH trial, 720 naive patients with advanced HCC were randomized to sorafenib plus erlotinib (n = 362) or placebo (n = 358). Median OS was similar in both sorafenib plus erlotinib and sorafenib plus placebo groups (9.5 v 8.5 months, respectively; hazard ratio [HR], 0.929; P = .408), as was median time to progression (3.2 v 4.0 months, respectively; HR, 1.135; P = .18). This combination did not significantly improve the OS of patients with advanced HCC [66].

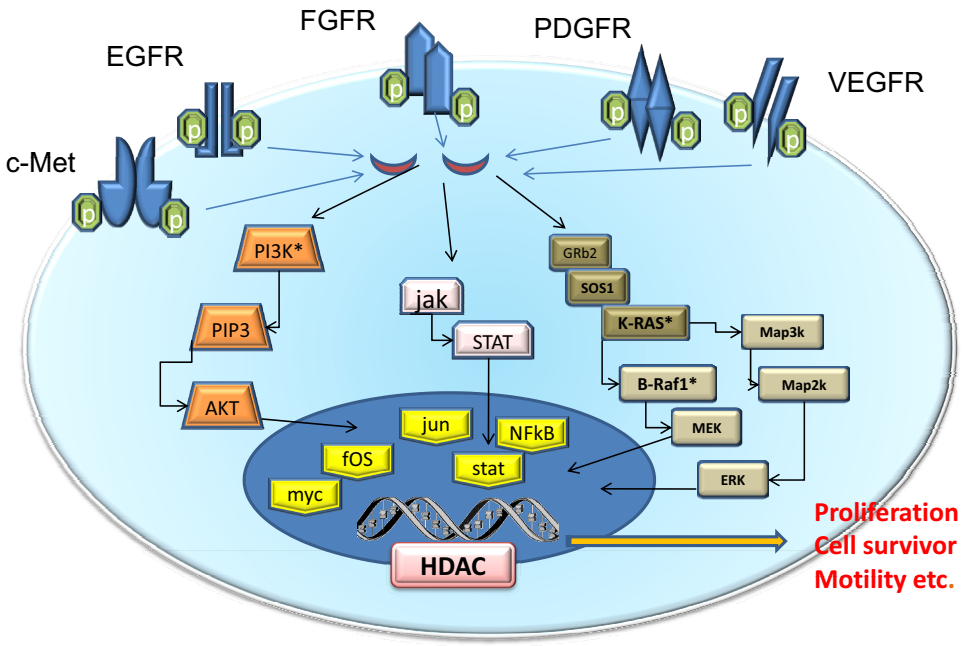

Fig. (1). Schematic pathway of the Tyrosine kinase proteins and their effect on cell proliferation, apoptosis, metastasis and angiogenesis. Receptors for growth factors (VEGFR, FGFR, PDGFR) activate intracellular receptor tyrosine kinases (RTKs) and the downstream RAS/RAF/mitogen-activated protein extracellular kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway, and promote the growth, migration and morphogenesis of vascular endothelial cells, thus increasing vascular permeability.

3.5. Everolimus

Everolimus is an oral inhibitor of mTOR pathway that is involved in tumor progression in preclinical HCC models [67]. In a recent phase III trial, EVOLVE- 1 (the first Everolimus for liver cancer evaluation) tested the efficacy of everolimus *vs* placebo (randomization 2:1) in patients with advanced HCC after the failure of sorafenib treatment. Median OS was similar in both groups (median OS, 7.6 months with everolimus, 7.3 months with placebo HR, 1.05; 95% CI, 0.86–1.27; p<0.68;) [68]. Thus ,everolimus is considered inactive in HCC patients.

4. MISCELLANEA

4.1. Cholangiocarcinoma (CCA)

It is difficult to obtain accurate worldwide incidence for CCA, particularly for discrepancies in classification methods in several countries. Cholangiocarcinoma (CCA) is a part of Biliary tract cancers (BTC) but, for the differences in their etiologic risk factors, pathogenesis, and molecular and genetic characteristics, each of these subtypes is considered a distinct biological entity [70, 71]. The current standard of care for patients with locally advanced or metastatic CCA is a combination of gemcitabine and cisplatin or alternative regimen as gemcitabine an oxaliplatin, or monotherapy with gemcitabine, capecitabine of 5-Fluorouracil in patients unfit for polichemotherapy [70-73]. Although several biological drugs have emerged as the standard treatments, alone or in combination, in many cancer types, in advanced cholangiocarcinoma (CCA), no targeted agents have demonstrated to have survival benefits. [74-76]. The reason of these difficulties in the progress of biological drug development in CCA is also due to the relatively low incidence of this disease and lack of industry support. There are only a few completed phase II/III studies assessing the early efficacy and safety of a few classes of targeted agents in CCA (Table **1**). These trials, including several subtypes of BTC (not only CCA) were conducted either as single agents, combined targeted agents, or in combination with CT regimens and has been limited to drugs targeting the EGFR, VEGF or its receptors and other angiogenesis molecules, MEK, and c-MET [77,78]. Unfortunately, none of these agents or regimens have definitively demonstrated a real survival benefit in CCA [85-90].

Recent studies have used whole transcriptome analysis, sequencing, and fluorescence in situ hybridization (FISH) to identify translocations involving the fibroblast growth factor receptor 2 (FGFR2) gene in 10–45% of ICC tumors [73,74,76, 80-84]. These translocations result in a novel fusion protein between the FGFR2 and several partners and some pharmacologic inhibitors are under study.

4.2. Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) represents 95% of all pancreatic cancers and is a lethal tumor. Its incidence and death rate are rising and patients are faced with extremely poor 5-year survival rates lower than 10% [91]. The poor prognosis of this tumor is due to late diagnosis, lack of adequate therapeutic options and failure to stratify clinical trials according to patients heterogeneity. The association of 5 – fluoruracil, irinotecan and oxaliplatin (FOLFIRINOX), gemcitabine and nab-paclitaxel, are the commonly used chemotherapies for PDAC [92-94]. Only a proportion of patients respond to these drugs and improvement in overall outcome, despite being statistically significant, is disappointingly small. Since it has become clear that no drug suits all PDAC patients, therapies are sought for specific molecular signature, hijacking successfully the

Table 2. Small molecule inhibitors currently used in phase III HCC.

Agent (Brand Name) *Antibody Type*	Molecular Target(s)	FDA-approved Indication(s)	Toxicities, Side Effects, and Precautions	Annotations
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	HCC -Renal cell cancer -Thyroid carcinoma	Hypertension; alopecia; bleeding; rash; hand-foot syndrome; hypophosphatemia; elevated amylase and lipase levels; myelo-suppression; wound-healing complications	VEGFR, PDGFR, Kit, BRAF cquired mutation for prevention resistance.
Brivanib (BMS-582664)	FGFR VEGFR	HCC	fatigue, hypertension, and diarrhea	down-regulation of cell cycle regulators, including cyclin D1, Cdk-2, Cdk-4, cyclin B1, and phospho-c-Myc
Sunitinib (Sutent)	VEGFR, PDGFR, c-KIT, FLT3	-Renal cell cancer, -GIST	yellow discoloration of skin; hypothyroidism; depression of LVEF; adrenal function abnormalities; myelosuppression; mucositis; elevated lipase and creatinine levels; elevated liver chemistries; increased uric acid levels	cquired mutation for prevention resistance. Genotype for CYP3A4. Dose reductions for CYP3A4 Poor Metabolizer (PM)
Erlotinib (Tarceva)	EGFR (HER1/ERBB1) positive	-NSCLC -Pancreatic cancer	Acneiform rash; loss of appetite; fatigue; conjunctivitis; elevated liver chemistries	EGFR protein expression Check CYP3A4*1B
Everolimus (Afinitor)	mTOR via EGFR	-Pancreatic neuroendocrine tumor -Renal cell carcinoma Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis -Breast cancer HR+, HER2-	stomatitis, infections, rash, fatigue, edema, abdominal pain, fever, asthenia, cough, headache and decreased appetite. Renal angiomyolipoma	EGFR exon 19 deletion or exon 21 substitution (L858R) positive
Tivantinib (ARQ 197)	c-MET high level	HCC	Mucositis, Palmar-plantar erythrodysthesia hypokaliemia, neutropenia	Check CYP2C19*2 and *3. Reduce dosing in Poor metabolizer

approaches applied to other tumors, *e.g.* EGFR inhibition of KRAS wild-type tumors in colorectal cancer [95] and treatment of HER2 amplified tumors with trastuzumab in breast cancer [96]. Unfortunately, similar drug approaches are applicable to relatively few cases of PDAC due to its mutational landscape being highly heterogeneous [97]. Several phase II and III clinical trials have investigated the combination of an anti-EGFR agent and CT for the treatment of advanced pancreatic cancer [98]. Historically, gemcitabine as single-agent has a little effect with a tumor response rates less than 10%. in patients with advanced PDAC, with median tumor progression of about 4 months, and median OS less than 6 months [99]. The addition of EGFR-targeted therapy to gemcitabine and other CT-regimens, in some phase II studies, can result in a potential survival benefit, but data are in contrast [103-106].

Phase 3 trials of anti-EGFR treatments have enrolled molecularly unselected populations of patients with both unresectable locally advanced and metastatic pancreatic cancer [101-104]. Despite intensive efforts, direct pharmacologic inhibition of KRAS has been unsuccessful because of the high binding affinity of the oncoprotein to GTP and inability to identify an easily accessible active site within KRAS that is susceptible to competitive allosteric inhibition [105]. A single phase III study (PA.3) has shown a modest (but statistically significant) survival benefit. In fact, the addition of erlotinib to gemcitabine gave a similar RR which was similar in erlotinib plus gemcitabine: 8.6%; placebo plus gemcitabine: 8.0%, but a showed prolongation of OS (HR 0.82; 95% CI 0.69-0.999; p= 0.038) and PFS (HR 0.77; 95%CI 0.64-0.92; p=0.004) [108] although these differences reflected a median improvement of only 10 and 6 days, respectively. Preclinical studies have shown additive effects of the combination of anti-EGFR agents and a VEGF-inhibitors [112,113], without a corresponding clinical benefit in clinical phase II studies of treatment-naïve advanced pancreatic cancer, combining gemcitabine-based chemotherapy with bevacizumab (an antibody directed against VEGF) and anti-EGFR therapy (cetuximab or erlotinib) [114-119].

CONCLUSION

In the last decades, the clinical impact on the treatment of gastrointestinal cancers has improved the outcome in some tumors regarding PFS and OS. Moreover, we think that this recent progress has provided a remarkable chance to identify prognostic and predictive markers of the efficacy of antiblastic treatments. Dynamic and agile clinical guidelines that reflect a rapidly changing knowledge base for decision-making support are needed to define clinically meaningful outcomes as precision medicine expands the definition of cancers, leading to increased demand for the use of targeted drugs as single agents or in combination. [127].

Genetic markers can be used to discriminate patients responders and exclude patients at high risk to develop severe toxicity, and eventually, adjust dosing [120]. Furthermore, the major obstacles for the consideration of the clinical laboratories (who are responsible for providing pharmacogenomics services), are: i) the availability of approved guidelines; ii) the current absence of public reimbursement; iii) the need for genotyping accuracy; and iv) the exigency to find clinical expertise to interpret correctly the results [116]. However, there exists a chronic inadequacy of education of both the physicians regarding pharmacogenomics test. The current knowledge of healthcare professionals regarding pharmacogenomics is still insufficient, and school curricula are only slowly including teaching of this subject in their courses. Pharmacogenomics knowledge is rapidly developing and changing, and it is imperative that healthcare professionals must be upgraded according to the advances and clinical indications [120]. Moreover, pharmacogenomics testing may support clinicians to screen patients who are more or less likely to benefit from expensive drugs and also prevent the delay of the correct alternative treatment [121]. Recently, several issues to assess the quality of cost-effectiveness in the cancer therapy managements have become available. An important example is the National Institute for Health and Clinical Excellence (NICE). NICE forms several clinical Advisory committees, which incite Pharma and Academic communities to bring robust data, including the design and data source, for economic models of personalized healthcare [122]. It is well known that molecular genetics counseling performed before selected cancer treatment provides lower overall medical costs and higher quality of life [123]. NICE, also provides a method for measuring Quality-Adjusted Life-Years (QUALYs); metrics that combine heterogenic information on outcomes, analytical, and cost-effectiveness for each treatment [124]. We believe that the right way to face these challenges is based on a multidisciplinary treatment approach and to rationalize the costs of these treatments due to aimed-interventions [125].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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